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Award Number: DAMD17-98-1-8321

TITLE: Viral Vectors Selective for Metastatic Breast Cancer Tumor Cells

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REPORT DATE: November 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release
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DTIC QUALITY INSPECTED 3

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 074-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE November 1999	3. REPORT TYPE AND DATES COVERED Annual (01 Oct 98 - 01 Oct 99)	
4. TITLE AND SUBTITLE Viral Vectors Selective for Metastatic Breast Cancer Tumor Cells			5. FUNDING NUMBERS DAMD17-98-1-8321	
6. AUTHOR(S) William Folk, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Missouri Columbia, Missouri 65211 e-mail: folkw@missouri.edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release distribution unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) <p>Breast cancer is the most common malignancy in American women, and its most life-threatening aspect is metastasis. There are presently no effective means to treat metastatic cancer, and novel therapies are required to eliminate metastatic cells and the consequent morbidity and mortality of breast cancer.</p> <p>We are developing polyomavirus gene therapy vectors which are capable of specifically targeting metastatic breast cancer cells. Selective targeting will result from the specific attachment of modified viruses to urokinase plasminogen activator (uPA) expressed on metastatic cells and to the selective expression of genes under the control of promoters which are preferentially activated in metastatic cells. These gene therapy vectors will be assembled from highly purified capsid proteins, histones and DNA and will be tested in human breast cancer cells in culture and in tumors.</p> <p>During the past year, we have modified the polyomavirus VP1 capsid protein to contain sequences of uPA capable of binding to the uPA receptors on tumor cells. We have obtained the requisite enzymes for assembling DNA into chromatin. The next year will be devoted to assembling virus-like particles with the modified capsid proteins and the chromatin, and to preparing to test them for specificity of adsorption to cancer cells.</p>				
14. SUBJECT TERMS Breast Cancer, IDEA			15. NUMBER OF PAGES 6	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

FOREWORD

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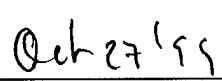
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Introduction

The most life-threatening aspect of cancer is its capacity to invade normal tissue and to establish new foci of tumor cells at distant sites. While there has been some progress in understanding some of the genetic and cellular mechanisms involved in the conversion of normal cells to metastatic tumor cells, little progress has been made in utilizing what has been learned of the molecular mechanisms of metastasis to reduce its impact upon morbidity and mortality. The objective of this work is to do that by developing novel gene therapy vectors selective for metastatic cells. Selectivity of the gene therapy vectors will rely upon metastatic cells expressing receptors to which the vectors can adsorb and upon the metastatic cells expressing signal transduction pathways which will activate vector gene expression.

Key Research Accomplishments — Reportable Outcomes

We are making the progress planned and described in the original application. Specifically:

Technical Objective 1:

We have constructed a polyomavirus vector with the firefly luciferase gene under the control of the viral enhancer and the viral promoters.

Technical Objective 2:

We have modified the polyomavirus VP1 protein to contain high affinity ligands for the uPA receptor. These are being expressed in *E. coli* and will then be placed in vectors capable of expression in insect cells. We will then measure the efficiency of capsomere formation and optimize capsid assembly with these proteins.

Technical Objective 3:

We have obtained the enzymatic machinery required to reconstruct chromatin with DNA containing the LUC gene under the control of the viral enhancer and during the next year will use it to reconstitute chromatin.